TCF7L1 suppresses primitive streak gene expression to support human embryonic stem cell pluripotency.

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Public Summary:
Human embryonic stem cells (hESCs) are exquisitely sensitive to WNT ligands, which rapidly cause differentiation. Therefore, hESC self-renewal requires robust mechanisms to keep the cells in a WNT inactive but responsive state. How they achieve this is largely unknown. We explored the role of transcriptional regulators of WNT signaling, the TCF/LEFs. As in mouse ESCs, TCF7L1 is the predominant family member expressed in hESCs. Genome-wide, it binds a gene cohort involved in primitive streak formation at gastrulation, including NODAL, BMP4 and WNT3 Comparing TCF7L1-bound sites with those bound by the WNT signaling effector beta-catenin indicates that TCF7L1 acts largely on the WNT signaling pathway. TCF7L1 overlaps less with the pluripotency regulators OCT4 and NANOG than in mouse ESCs. Gain- and loss-of-function studies indicate that TCF7L1 suppresses gene cohorts expressed in the primitive streak. Interestingly, we find that BMP4, another driver of hESC differentiation, downregulates TCF7L1, providing a mechanism of BMP and WNT pathway intersection. Together, our studies indicate that TCF7L1 plays a major role in maintaining hESC pluripotency, which has implications for human development during gastrulation.

Scientific Abstract:
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